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TERMINAL PROGRAMS IN THE GRADUATE SCHOOLS

By Dr. CARL E. SEASHORE

THE STATE UNIVERSITY OF IOWA

A TERMINAL program leading to the master's degree is a program of study designed specifically on a one- or two-year basis as distinguished from the master's degree program leading toward the doctorate, which is designed for the first year on a three-year basis.

The terminal program is tailor-made, designed to fit the individual needs of the student in relation to personal and professional objectives. It is sponsored by a professor who gives particular attention to the organization of terminal programs. It, therefore, becomes student-centered as opposed to subject-centered. It represents a vocational or semi-professional bent but should be distinguished from purely technological courses and be dominantly of a liberal character but with a vocational aim. The member of the staff who directs the work takes responsibility for the maintaining of standards and a happy balance between concentration in an area and reasonable spread of work within a chosen field, the securing of the privileges involved and personal direction of the thesis. The work on the thesis and the organized reading are designed to introduce the student to bona-fide graduate methods of study. The terminal program ensures adequate consultation between student and staff at the time of registration and personal guidance throughout toward a well-conceived objective.

The primary purpose of this type of organization is the standardization of two types of master's de-

grees. The appropriate implementation of this organization will indicate to the world that universities now recognize a double function: (1) furnishing the highest preparation for a scholarly career for which the doctorate represents the conventional standard and (2) preparing for useful occupations and citizenship, and enrichment of the good life, through one or two years of liberal studies at the graduate level. Incidentally the terminal program may serve as a proving ground for students who discover themselves in this work and then transfer, duly motivated, to the standard plan.

The doctorate has been the center of interest and pride over standards in the graduate schools up to date and the master's degree has been treated in a very slipshod manner as an unnecessary step, as requiring work which does not belong in the graduate school, as drawing an inferior class of students and as merely another undergraduate year. It is safe to predict that in the near future the graduate schools will have ten or fifteen times as many candidates for the master's degree as for the doctorate. It is, therefore, high time that these schools evaluate their objectives in order to offer adequate facilities and fair treatment to good students who wish to plan a one-year program, by recognizing their responsibility of preparing for citizenship and useful living at this level.

For the purpose of maintaining adequate standards, freedom in adjusting the program to the needs of the student, discriminating educational guidance, and conservation of the time and energy of the faculty, there should be a threefold choice for routing students in the graduate schools. At the time of admission the student may be given a choice of one of three plans to be followed: (A) the Standard plan, specifically designed for the maintenance of liberal and rigorous standards leading to the traditional advanced degrees, (B) the Terminal plan, providing for specially designed terminal schedules leading to the master's degree, and (C) the Free-lance plan, not leading to any degree. The student may be given the choice by his own tentative declaration at the time of first registration, and readjustments in the choice of plan may be made later on the basis of accumulating experience and achievements. The record of choice can be kept by merely writing Plan A, Plan B, or Plan C in a corner of the registration card.[1]

The separation of the standard and the terminal masters' degrees will be a reciprocal advantage. The standard degree can then be used as a certificate of clearance for the doctorate, whereas the terminal degree can be used as a record of general education or a certificate of qualifications for a specific occupation. Each calls for a different type of direction and staff interests, although the standards for admission and candidacy for a degree should be the same for both. The old notion that a student who needs only a master's degree as certification for his job is an inferior student should be abandoned and high standards of achievement should be maintained. The standard graduate schools should take the lead in setting up a model for the terminal degree which can be adopted by the best colleges that are competent to offer specific terminal programs.

[1] From "Three-Way Organization in the Graduate School," *Journal of Higher Education*, 15: 7, October, 1944.

Some Reasons for the Organization of Terminal Programs

In recent years certain very radical changes have taken place which indicate the necessity for standardizing a master's degree and providing for the encouragement and direction of graduate work for students who are not going to proceed to the doctorate. Among these are the following:

Rise in Educational Level. The enrolment in our secondary schools has increased more than 4,000 per cent. since 1880. Registrations in colleges and universities have increased, similarly, by leaps and bounds. For practical purposes a college education is no more now than a high-school education was a few years ago. The doctorate is more commonplace now than the bachelor's degree was fifty years ago. There are now more post-doctorate students in the universities than there were candidates for the doctorate at the beginning of the century. There have been corresponding advances in professional and technological training. Standards for the doctorate and professional degrees are well established, but there is now urgent need for organization of graduate work at the level of the master's degree to meet the demands of mass education at the graduate level. This takes the form of terminal programs.

Semi-Professional and Vocational Demands. The American college was launched to provide for three professions—law, medicine and the ministry. Out of this beginning has come our vast program of liberal education. But we now recognize that the pursuit of pure arts and science has taken on a professional, vocational and avocational aspect, as in research, teaching, the applied arts, government and industry. As Professor Whitehead has said, there is no place in higher education for learning that is not useful. The master's degree has too long been looked upon as an ornament. There is, therefore, demand for liberal curricula that have a practical trend in time-limited programs.

Progress in Science and Technology. The undergraduate advance in the humanities, pure sciences and technology must be paralleled by provision for the

pursuit of them at the graduate level on the part of large masses of students. With a vast increase in demand for graduate work, it is essential that we distinguish between those who are to become scholars at the doctoral level and the much larger group of those who are entitled to well-considered plans at the level of the master's degree.

Leisure and Unemployment. The new-found leisure demands higher education for leisure. The increasing unemployment arouses cravings for training at higher and higher levels, for the enrichment of personality, the cultivation of avocational activities and a larger and larger share in the good life. Thus the demand for education for leisure is finding a place in liberal education at the graduate level.

Increase of Wealth. The increasing national and personal wealth demands expansion in scientific technology. We have seen these demands rise from the trade school, the vocational high school and technological institutes at the college level, and we are now called upon to make provision for the liberalizing of the technologies by creating love of knowledge and increasing the power for research through graduate study. The increase of wealth makes it possible to employ semi-expert technicians in every area for the advancement of knowledge and professional services.

The Spread of Knowledge. The phenomenal spread of knowledge in modern times has led to the lengthening of the standard periods for education. There is a cry for leadership on a higher and higher scale in the implementation of growing knowledge in every field of human activity. This involves not only vocational training but a distinct liberalizing of the vocational and technological point of view which demands the facilities of the graduate school.

Social, Moral and Political Intelligence. We are now in the midst of the expression of democracy and preparation for the defense of democracy. There is a growing demand from all walks of life for a certain amount of orientation for leadership at the graduate level. The feeling of need of education for citizenship, and particularly for leadership, in the organization of peace at home and abroad is vitalizing graduate study and diverting scholarly interests from the purely intellectual pursuits to the organization of knowledge for the exercise of citizenship from the level of home-making to that of countless forms of high public service. Master's theses are being written as self-orientation for jobs.

Adult Education. Not only do students move on to higher and higher levels for a capstone over their undergraduate education but adults in all walks of life are beginning to recognize the need and the facilities for the type of orientation they can secure at the graduate level without necessarily proceeding to the doctorate. Recent science has demonstrated that adults in advanced occupations can learn as well as students in college. The craving for keeping intellectually alive is going to draw many mature people into the graduate schools.

The Fine Arts. The cultivation of the fine arts has now moved into the graduate schools, whether pursued as a profession or as an avocation. Students, young and old, are going to come to the universities as clearing-houses for the cultivation of the fine arts, the master's degree being required for teaching in the high schools and similar training being necessary for all types of communal activities and developments. Painters, composers, poets, playwrights and players are finding a new door open for the advancement of their learning. Universities have given but little attention to direct research on the application of the fine arts, but all the above characteristics of the present day tend to bring them to the front in a planful approach to the application of principles of beauty in useful objects and situations throughout life.

FIELDS FOR TERMINAL PROGRAMS

Practically every department in a university is now giving instruction of the general type here recommended, but only half-heartedly encouraged or organized. It would be very easy to set up formally fifty or a hundred specific programs which could be recommended in a standard university: such as courses certifying the requirements in many specific branches of education, engineering, social service, physical and biological sciences, psychometry and clinical psychology, and a large number of new types of training for technicians in medicine, fine arts, journalism, law and commerce. Then there is a large number of students who have no vocational interest but can only give a year or two to liberal graduate work which ought to be designed with some care.

I would not encourage the cluttering of catalogues with such detailed announcements, but would publish an announcement for entering students somewhat to this effect:

> There are no fixed curricula leading to the terminal master's degree. Each student's program is designed so as to take into account the qualifications, needs, and aspirations of the individual for the limited time available. At registration time the student indicates to the Dean of the College the general character of his plans and purposes. The Dean then introduces him to the member of the faculty who would be most competent as a consultant for the direction of the work planned, taking all relevant factors into account and serving as educational guide in the program.

OBITUARY

ROSCOE GILKEY DICKINSON
1894–1945

PROFESSOR ROSCOE GILKEY DICKINSON, who had been a member of the staff of the California Institute of Technology since 1917, died in Pasadena on July 13, 1945, after a short illness.

Professor Dickinson, who in recent years had been professor of physical chemistry and acting dean of the Graduate School at the California Institute of Technology, was the first man to receive a doctor's degree from this Institute. He was born in Brewer, Maine, on June 10, 1894, and his undergraduate work, in the field of chemical engineering, was carried on at the Massachusetts Institute of Technology, from which he received the degree S.B. in 1915. After two years as graduate assistant and research fellow at M. I. T., he accepted appointment as instructor in inorganic chemistry at the California Institute (then the Throop College of Technology), and after three years, in 1920, he was awarded the doctor of philosophy degree for his work on the structure of complex crystals. He was a National Research Fellow in Chemistry for three years, and a Fellow of the International Education Board for one year, 1924–25.

Professor Dickinson's early investigations of the structure of complex crystals by the use of x-rays were carried out with the use of methods which he had in considerable part developed, at a time when the lack of quantitative information about the interaction of x-rays and crystals made the task of the crystal structure investigator a difficult one. Dickinson's analyses, which were made with great care, have been found to be completely reliable; he determined the structures of a number of complex crystals, including the chlorostannates, the chloropalladites and platinites, the complex cyanides of zinc and mercury, tin tetraiodide and hexamethylenetetramine. His determination of the structure of hexamethylenetetramine was the first structure determination made of an organic substance by the x-ray method.

During the past twenty years he and his collaborators carried on many researches in the field of photochemistry and chemical kinetics. He was one of the pioneer investigators of the Raman spectra of ions and gas molecules, the properties of neutrons, and the use of radioactive indicators in the investigation of chemical reactions.

Professor Dickinson was closely connected with Arthur A. Noyes in the early days of the California Institute of Technology in determining the nature of the Institute, especially with respect to advanced study and research, and his influence was continued in later years through his service as chairman of the committee on graduate study and research of the Division of Chemistry and Chemical Engineering. His untimely death is a serious loss to science.

LINUS PAULING

ALBERT EDWARD EDGECOMBE
1897–1945

IT is given to some men to live well beyond the allotted life span of "three-score years and ten," while others put away their test-tubes, culture media and microscopes much too early—or so it seems to us. In the latter group may be placed Professor Albert Edward Edgecombe, who died at the age of forty-eight years.

Mr. Edgecombe was born in Devonshire, England, on February 5, 1897, and succumbed to a cerebral hemorrhage at his home in Wilmette, Illinois, on March 30, 1945. He was the son of Samuel and Frances (Pennell) Edgecombe, coming to Canada with his parents when three years old. He taught in the secondary schools of Canada for several years, and served as a field agent of the Presbyterian Church in British Columbia. He was graduated with honors from Queens University, Ontario, in 1923 and received the degree of master of arts from the same institution two years later. He then entered the graduate school of the University of Chicago, completing the work for the doctorate in 1929. From the Chicago Law School he received the LL.B. and J.D. degrees in 1934. He became an American citizen in 1935.

In 1929 he joined the staff of the department of botany at Northwestern University as an assistant professor. Promotion to an associate professorship came in 1939. His special field of interest was mycology, although his broad botanical training enabled him to teach a variety of courses. He was greatly interested in certain dermatophytic fungi, and had extensive cultural work under way at the time of his death. He spent nine summers in advanced study at such institutions as Cornell University, the University of Michigan, Pennsylvania State College, the Gradwohl Biological Laboratory and the Presbyterian Hospital of Columbia University.

Dr. Edgecombe was a fellow of the American Association for the Advancement of Science, a charter member of the Mycological Society of America, and a member of Phytopathological Society, Botanical Society, American Association of University Professors, Sigma Xi, Phi Alpha Delta and the Illinois Academy of Science. He married Sara Roberta Mohn, of Pottstown, Pennsylvania, on November 23,

1939. His widow and daughter Phyllis, together with a brother who resides in Canada, survive him.

Professor Edgecombe was a quiet, self-effacing man with a high regard for the truth, as he saw it, both in his scientific investigations and in his dealings with his fellow man. He was essentially a very religious man, although not an active participant in religious activities in his maturer years. He believed so strongly in the tenets of right living and peace that such holocausts as World War II were to him well-nigh incomprehensible and inexplicable. He was first stricken in February, but carried on by sheer courage and determination until the day of his death. His adult life might be accurately epitomized by the statement of his belief that assiduity should be the principal criterion for success.

HANFORD TIFFANY

RECENT DEATHS

CHARLES LOUIS POLLARD, the botanist, librarian of the Martha Canfield Free Library at Arlington, Vt., died on August 16 at the age of seventy-three years.

DR. GEORGE RAYMOND GAGE, professor of botany at Vanderbilt University, died on August 18 at the age of fifty-five years.

DR. CHARLES B. WING, emeritus professor of structural engineering at Stanford University, died on August 23 at the age of eighty-one years.

DR. HUGH HAMPTON YOUNG, surgeon and neurologist at the Johns Hopkins Hospital, died on August 23. He was seventy-four years old.

IT is reported that Dr. Hans Przibram, of the department of experimental zoology at the University of Vienna, has died of hunger in a concentration camp.

DR. H. S. VAN KLOOSTER writes to SCIENCE that "Professor Ernst Cohen, emeritus professor of physical chemistry and formerly director of the Van't Hoff laboratory in Utrecht, Holland, died in Germany sometime in September, 1944. The cause of his death and the place where he died are not known. After having been apprehended early in 1943 and released shortly afterwards, he was again arrested in March, 1944, and transported to Germany. Thus disappeared in his seventy-fifth year a noted Dutch scientist, well known to many American chemists, who after the first World War had made strenuous efforts to re-establish relations between Germany and her erstwhile enemies in the field of science."

SCIENTIFIC EVENTS

RESEARCH FELLOWSHIPS FOR INDIA

IT is reported in *The Times*, London, that Lord McGowan has written to Professor Wadia, president of the National Institute of Sciences of India, offering on behalf of the Imperial Chemical Industries (India) a number of research fellowships for the encouragement of Indians in chemistry, physics and biology, to be held at Indian universities and institutions. The sum offered is 336,000 rupees—equivalent to £25,200—over the next five to seven years.

In his letter Lord McGowan states:

> The National Institute of Sciences is, we believe, destined to play in India a part similar to that which the Royal Society of London has performed for nearly 300 years in leading the scientific progress of this country. The Royal Society until recent years was hampered by lack of funds and provision for the maintenance of scientific workers. This difficulty was eventually overcome by the generosity of various benefactors, including industrialists such as Mond and Messel. We thought, therefore, that there could be no better way of encouraging the advance of science in India and with it the general prosperity of the country than by the offer of these fellowships which under the wise administration of your council will, we hope, lead to an augmentation of the distinguished successes in science already attained by so many of your fellow countrymen.
>
> Each fellowship will be worth 400 rupees a month and will be tenable in the first instance for two years, with a possibility of extension up to three years. In addition there will be a grant for research expenses to be made to the fellowship-holders according to their needs of special apparatus and materials. For this purpose the National Institute will have at their disposal an average of 600 rupees per annum for each fellowship.
>
> There will be a grant of 13,200 rupees a year to the National Institute for five years to enable them to pay for administration and the travelling expenses of such fellows of the institute as may be selected to visit the fellowship-holders at their universities or institutions.

The fellowships will be open to persons, irrespective of sex, race or religion, resident or domiciled in India (British India or the States), and under thirty-five years of age.

PLANT BREEDING AT CORNELL UNIVERSITY

THE Cooperative Grange League Federation Exchange, Inc., with headquarters at Ithaca, New York, has made available to Cornell University, through and

on behalf of the New York State College of Agriculture, grants amounting to approximately $10,000 per year for the furtherance of investigations in the Department of Plant Breeding. These grants are made for two purposes: (1) the breeding and testing of forage plants for New York State and vicinity, with major emphasis on those species which appear to have special value in providing greater growth during the summer season of normally low production, and (2) production of new grain corn hybrids and the increase and distribution of foundation seed stocks of the hybrids most desirable for New York State and adjacent areas. The work with forage crops is under the direction of Dr. S. S. Atwood, in cooperation with Dr. H. A. MacDonald, of the department of agronomy, and the research with hybrid corn is conducted by Dr. R. G. Wiggans. Provision is made for two graduate assistantships in each project.

These grants, as well as the grant made previously by this organization for research with small grains under the direction of Dr. H. H. Love, of the department of plant breeding, make possible considerable expansion of important investigations in the field of crop improvement.

GEOGRAPHY AT SYRACUSE UNIVERSITY

DR. PRESTON E. JAMES, who has been at the University of Michigan since 1923, except for the past four years when he has been in Washington with the Office of Strategic Services, first as chief of the Latin American Division and later as assistant chief of the Europe-Africa Division, has been appointed professor of geography at Syracuse University. He holds the rank of Lieutenant Colonel in the U. S. Army.

Richard Edes Harrison has been appointed on a part-time basis as lecturer on map-making.

Professor George B. Cressey will spend the coming academic year on leave at Stanford University, where he will assist in the development of a new Pacific-Asiatic-Soviet program.

The staff also includes Professor Eric H. Faigle, recently promoted to associate dean of the College of Liberal Arts, specializing on Canada; and Miss Eleanor E. Hanlon, acting as chairman of the department for 1945–46. Two members of the department are still on military leave, Professor Sidman P. Poole and Professor Joseph A. Russell. Colonel Poole and Lieutenant Colonel Russell are serving in the Topographic Branch of Military Intelligence in the Pentagon Building. Their major interests are the geography of Europe and of the Pacific, respectively.

With the enlarged staff, the new program of the university is designed (a) to contribute to the liberal education and international thinking of undergraduates, (b) to provide unsurpassed professional training to the doctorate in a few fields, (c) to promote geographic research and publication, and (d) to serve the needs of business, public policy and international relations.

SCIENTIFIC MEN ABROAD

A LETTER has been received by Professor A. B. Garrett, of the Ohio State University, from Dr. Jannick Bjerrum, of Copenhagen. It reads in part: "Here in Denmark we feel very happy in getting rid of the Germans and we are very thankful to the allied forces, who gave us our freedom again. As a whole, Denmark has escaped relatively well from the war. Our university activities went on quite regularly until that day in September, 1944, when the Germans arrested our police, and the students went home or underground. Now we are busy in making up for lost time and are giving extra lessons. In the autumn several hundred Norwegian students and some few Dutch will study here. In both these countries the universities have been closed for a long time. Here in Denmark we are very anxious to get our English and American periodicals for the last four to five years. We do not know much about the scientific news from your country."

Dr. Wm. Randolph Taylor, University of Michigan, has received a letter from Professor Henrik Printz indicating that he has come through the five difficult years in Norway fairly well and is anxious to reestablish scientific contacts abroad. Professor Printz is widely known for his work on the "green" algae. Dr. Taylor has also received a card from Dr. Rolf Grönblad, Karis, Finland, who writes that he and his scientific collections are all right. He wishes to reopen communication with American students of Desmids, for which large groups of algae he is a foremost authority.

Dr. Harold Kirby, professor of biology at the University of California at Berkeley, writes to SCIENCE that Professor Pierre P. Grassé has sent information that the laboratory of Wimereux was completely destroyed by the Nazis in 1942. The library, which had been a rich one, was reduced to ashes.

Dr. Edgar Lederer, chemist, Paris, is living at Lyon and working in Professor Fromageot's laboratory. This laboratory was missed by ten yards by a bomb but has been rebuilt since.

SCIENTIFIC NOTES AND NEWS

DR. GEORGE B. PEGRAM, professor of physics and dean of the Graduate School of Columbia University, will become acting president of the university when the resignation of Dr. Nicholas Murray Butler becomes effective on October 1.

SIR ALEXANDER FLEMING, the discoverer of penicillin, has been elected an honorary member of the Philadelphia College of Pharmacy and Science.

THE Illuminating Engineering Society has awarded its gold medal to Preston S. Millar, president of the Electrical Testing Laboratories, Inc., for his contributions to illuminating engineering.

DR. J. C. GEIGER has been nominated by the Executive Council of the Egyptian Public Health Association as honorary vice-president of the association.

MISS MABEL COLCORD, for over thirty-five years librarian of the United States Bureau of Entomology and Plant Quarantine, and who later served as chief of the entomological work of the Library of the Department of Agriculture, has been elected a member of Phi Beta Kappa. This action was taken in recognition of her high attainments in liberal scholarship and with particular reference to the compilation of the "Index to the Literature of American Economic Entomology" from 1915 through 1939. Miss Colcord retired from active duty on June 30, 1942.

A RECEPTION was held on August 21 at Columbia University under the auspices of the American-Soviet Science Society in honor of those who had attended the recent scientific congress in Moscow. These included Dr. Irving Langmuir, Dr. Harlow Shapley, Dr. Detlev W. Bronk, Dr. Jacob Heiman, cancer research specialist, Dr. Arthur Upham Pope, of the Iranian Institute, and Dr. Arpad L. Nadai, of the Westinghouse Laboratory. Dr. Leslie C. Dunn, of Columbia University, chairman of the American-Soviet Science Society, presided. Three hundred attended the reception.

THE honorary degree of doctor of science has been conferred by the University of Oxford on Professor H. M. Turnbull, professor of morbid anatomy in the University of London and director of the Pathological Institute of the London Hospital.

DR. ROBERT A. MILLIKAN retired on August 20 as administrative head of the California Institute of Technology, where since 1921 he has been chairman of the Executive Council of the institute. He will become a member of the board of trustees and its vice-president, and will assist the president of the board, James R. Page, in public relations and institutional development. He plans to continue his research work. Dr. Max Mason, formerly president of the University of Chicago, has retired from the Executive Council. He will continue as chairman of the Observatory Council and expects to resume work on the 200-inch telescope for the Palomar Observatory.

DR. ARTHUR C. COPE, professor of chemistry at the Massachusetts Institute of Technology, has been appointed head of the department. He succeeds Frederick G. Keyes, who has asked to be relieved of administrative work in order to devote his time to research in physical chemistry.

DR. JAMES G. POTTER, for a number of years head of the department of physics of the South Dakota School of Mines and Technology, and more recently physicist for the Bell Telephone Laboratories, has been appointed head of the department of physics of the Agricultural and Mechanical College of Texas at College Station. He will take up this work on September 1.

DR. HORACE W. DAVENPORT, associate in physiology of the Harvard Medical School, has been appointed professor and head of the department of physiology of the University of Utah.

DR. H. FREDERIC BOHNENBLUST, associate professor at Princeton University, has been appointed professor of mathematics at Indiana University.

DR. GORDON L. WALLS, of the scientific bureau of the Bausch and Lomb Optical Company, Rochester, N. Y., has been appointed for one year a research associate in the department of psychology of the University of Rochester. Dr. Walls plans to continue his work with the optical company.

PROFESSOR A. C. HARDY, regius professor of natural history in the University of Aberdeen, has been appointed Linacre professor of zoology and comparative anatomy in the University of Oxford.

JAMES A. REYNIERS, on leave for active duty in the United States Naval Reserve, has returned to the University of Notre Dame as research professor of bacteriology and director of the laboratories of bacteriology.

DR. IRENE MANTON, lecturer in botany in the University of Manchester, has been appointed professor of botany in the University of Leeds, in succession to the late Professor J. H. Priestley.

AT the University of London, Dr. D. H. Hey, since 1941 director of research at the British Schering Research Institute, has been appointed to the university chair of chemistry tenable at King's College; Professor C. Daryll Forde, to the university chair of

anthropology, and D. W. Harding, special lecturer in psychology in the University of Manchester, to the chair of psychology tenable at Bedford College. The title of reader in bacteriology has been conferred on J. C. Cruickshank, in respect of the post now held by him at the London School of Hygiene and Tropical Medicine.

LIEUTENANT COMMANDER GORDON A. ATWATER, head of the Navigation Department of the Naval Training School Advanced at Fort Schuyler, has been appointed chairman and curator of the department of astronomy and the Hayden Planetarium of the American Museum of Natural History. Commander Atwater has been released from active duty with the U. S. Navy as of September 1, when he will take over the direction of the Planetarium, its public performances and its program of instruction in celestial navigation for the armed forces.

DR. H. A. K. WHITNEY, chief pharmacist of the University Hospitals of the University of Michigan, has accepted an appointment as director of pharmaceutical development with the Ortho Research Foundation, Linden, N. J.

F. S. RUSSELL has been appointed by the Council of the British Marine Biological Association to be director of the laboratory of the association at Plymouth, England, in succession to the late Dr. Stanley Kemp. Mr. Russell has been a member of the staff since 1921.

LIEUTENANT COLONEL JOHN H. BELKNAP, chairman of the Division of Engineering of the University of Rochester, has been assigned to duty with the U. S. Group Control Council in Germany as deputy chief of the Electrical and Communications Branch. He will be in charge of generation, transmission and utilization of electrical energy and the associated communications within the American zone of occupation. While in Germany, Colonel Belknap also will make a study of industrial manpower and the utilization of research and engineering skill within the Allied and enemy countries.

DR. CHARLES M. CARPENTER, associate professor of bacteriology and public health at the Medical School of the University of Rochester, has been sent to the Philippine Islands on a special medical mission by the U. S. Office of Scientific Research and Development. In cooperation with the U. S. Army Medical Corps, he will make an investigation on venereal diseases, on which he is a special consultant for the U. S. Public Health Service.

THE thirtieth annual meeting of the Optical Society of America will be held at the Hotel Pennsylvania, New York City, on October 18, 19 and 20. Because of existing travel conditions, it has seemed inadvisable to apply to the War Committee on Conventions for permission to hold the usual type of meeting. Instead, since there is no objection to the holding of a local meeting which draws its attendance from the metropolitan commuting zone, the forthcoming meeting will be of this character. The travel restrictions do not apply to officers of the society whose presence is required for the purpose of conducting society business, nor to the speakers at the several sessions.

WESTERN RESERVE UNIVERSITY has received appropriations from the Beaumont Foundation of $200,000 and $20,000. Half of the larger gift will be applied toward the cost of a new building to be constructed by the School of Applied Social Sciences, at an ultimate outlay by the university of approximately $500,000. The remainder will be devoted to research work in the department of pathology. The gift of $20,000 will be applied to help to finance a project to be undertaken jointly by Western Reserve University and the Cleveland Hearing and Speech Center, for completing the remodeling of the new headquarters of the center and for research and the training of teachers in speech and hearing.

THE first graduating class of the four-year School of Medicine of the University of Utah has contributed $2,850 to establish and incorporate the Utah Medical Foundation. "The object and purpose of this corporation shall be: To promote the cooperation of alumni and friends of the School of Medicine of the University of Utah in improving the undergraduate, graduate and research functions of that institution; to establish scholarships, lectureships, professorships, research and student loan funds in that institution. . . ." The foundation has established the Dr. W. R. Tyndale Lectureship in Medicine. Dr. George W. Thorn, Hersey professor of the theory and practice of physic of the Harvard Medical School, was the first lecturer. He discussed "The Role of Endocrine Glands in Adaptation" and "Fatigue of Thyroid and Adrenal Origin."

The Experiment Station Record reports that a committee appointed by the New York State Conference Board of Farm Organizations is endeavoring to raise $100,000 for a Memorial Fund to establish fellowships of $200 each in the College of Agriculture of Cornell University in memory of the late Dean Carl E. Ladd.

THE Department of Scientific and Industrial Research has made to the British Cotton Industry Research Association at Shirley Institute, Manchester, a grant of £30,000 a year for five years if the industrial income of the association reaches £70,000 a year, and an additional pound for pound grant on all industrial

income over this amount to a maximum of £50,000 a year. Dr. F. C. Toye, director of the institute, said that it was proposed to set up an engineering department the results from which would have considerable influence on the design and development of textile machinery.

THE central editorial offices of *The American Journal of Psychology* have been removed from Cornell University to the California Institute of Technology at Pasadena. Professor Madison Bentley continues as responsible editor. The business office remains at Morrill Hall, Ithaca, N. Y.

THE American Standards Association has published a new Safety Color Code for Marking Physical Hazards developed by one of its war committees. The purpose of this code is to unify on a national scale the colored markings used to warn employees of certain physical dangers to be avoided, to mark the location of safety equipment and to identify other protective equipment. The standard is a codification of certain already recognized concepts regarding use of color for safety purposes. Much of the standard deals with suggested applications for these colors such as the marking of safety cans, fire sirens, posts, hand rails, unguarded edges of platforms, location of gas masks, stretchers, etc. The investigation was undertaken at the specific request of the War Department, but it also has a wide application in industry. Neither the War Department nor industry intends to use color markings as a substitute for adequate guards or other safety measures, but to supplement them. The American Standards Association will welcome comments on: (1) difficulties that arise in using the standard, and (2) exceptionally good results from its use.

SPECIAL ARTICLES

QUANTITATIVE ACTION OF PENICILLIN INHIBITOR FROM PENICILLIN-RESISTANT STRAINS OF STAPHYLOCOCCI[1,2]

A POTENT inhibitor of penicillin has been obtained by Kirby[3,4] from coagulase-positive strains of staphylococci which were naturally resistant to penicillin. We have extended this observation and have shown that strains of staphylococci made resistant to penicillin *in vitro* do not produce a penicillin inhibitor, but strains which have become resistant in the human body following the administration of penicillin yield a potent inhibitor of penicillin.[5] This suggested to us a similarity between the development of resistance of staphylococci to the sulfonamides and to penicillin, though the underlying mechanism may differ.[6] The purpose of this preliminary report is to show that the degree of resistance which a group of selected strains of staphylococci has for penicillin, as measured *in vitro,* is quantitatively related to the penicillin inhibitor produced by these strains; that is, the greater the resistance, the more potent is the inhibitor. Furthermore, crude inhibitor prepared from resistant strains of staphylococci will inactivate varying concentrations of penicillin over a period of time in a quantitative manner, the time required for the inactivation being dependent upon the amounts of inhibitor and concentrations of penicillin which are used.

[1] From the Division of Internal Medicine, University of Minnesota Hospitals and Medical School, Minneapolis.

[2] Supported by grants from Sharp and Dohme, Inc.; The Graduate School, University of Minnesota; and from the Committee on Scientific Research, American Medical Association.

[3] W. M. M. Kirby, SCIENCE, 99: 452, 1944.

[4] *Idem, Jour. Clin. Invest.*, 24: 170, 1945.

[5] W. W. Spink and V. Ferris, *Proc. Soc. Exp. Biol. and Med.* (in press).

METHODS

Source of Strains. Seven strains of coagulase-positive staphylococci isolated from human patients were studied. Five of these strains had apparently become resistant in the body as a result of therapy with penicillin, since organisms obtained from the same lesions prior to treatment were sensitive to penicillin. The two remaining strains had not been previously exposed to penicillin and displayed a natural resistance to penicillin. We are indebted to Dr. Donald G. Anderson of Boston for providing us with three strains.

Determination of in vitro sensitivity to penicillin. The sensitivity of the strains of staphylococci to sodium penicillin was determined in the following manner: each of the strains was grown for two to three generations in Gladstone's synthetic and water-clear medium, the preparation of which has been described elsewhere.[7] Then 0.1 ml of a 10^{-3} dilution of a 24-hour culture was seeded to each of several tubes containing Gladstone's medium. The final volume of each tube was 10 ml. Poured plates indicated that such an inoculum contained approximately from 300,000 to 900,000 organisms. Freshly prepared aqueous solutions of commercial sodium penicillin were added in increasing concentrations to the series of tubes containing the bacterial suspensions. Incubation at 37 degrees C. was then carried out for 48 hours. The amount of penicillin necessary to inhibit growth completely was ascertained by selecting that tube which revealed no turbidity with the lowest concentration of penicillin.

[6] W. W. Spink, L. D. Wright, J. J. Vivino and H. R. Skeggs, *Jour. Exp. Med.*, 79: 331, 1944.

[7] W. W. Spink and J. J. Vivino, *Jour. Clin. Invest.*, 23: 267, 1944.

Determination of potency of penicillin inhibitor. The potency of penicillin inhibitor produced by each strain was defined as follows: crude inhibitor was obtained from a 24-hour culture grown on agar plates by extracting a concentrated suspension of organisms with acetone and ether according to the method of Harper[8] as described by him for the paracolon bacillus. The extracted bacteria were then dried and tested for sterility. Then 0.1 ml of a 10^{-3} dilution of a 24-hour culture of staphylococcus, which had been previously established as being sensitive to penicillin, was added to each of several tubes with Gladstone's medium and increasing concentrations of sodium penicillin. Either 0.01 or 0.1 mg per ml of dried bacteria, depending upon the potency of the inhibitor, was added to the tubes which were then left at 37 degrees C. for 48 hours. The tube showing bacterial growth with the highest concentration of penicillin indicated the number of units of the antibiotic which were inactivated by the given quantity of dried bacteria.

Quantitative action of penicillin inhibitor. The quantitative action of inhibitor was resolved by the following method: the same amount of dried bacteria was added to each of several sterile and standardized colorimetric tubes containing the foregoing inoculum of a 24-hour culture of a strain of penicillin-sensitive staphylococcus and increasing concentrations of sodium penicillin. Growth curves of the organisms were then made by incubating the contents at 37 degrees C. and measuring the density of the bacterial culture in the Evelyn photoelectric colorimeter with a 540 filter at appropriate time intervals over a period of 60 hours. A similar series of observations were made by using varying amounts of dried bacteria and the same concentration of penicillin in each tube. Repeated observations were carried out with different sources of commercial penicillin, including 8 preparations of sodium penicillin, 2 of calcium penicillin and 2 of ammonium penicillin.

RESULTS

The results of a representative series of observations on the resistance *in vitro* of 7 strains of coagulase-positive staphylococci to the same lot of sodium penicillin are presented in Table 1. The number of units of penicillin necessary to inhibit growth completely varied from 0.6 to 20 units per mil. For comparison, the inhibitory effect of 0.01 or 0.1 mgr per ml of dried bacteria obtained from these strains upon the action of penicillin against a penicillin-sensitive strain of staphylococcus is presented. It is to be noted that 800 units of penicillin per ml were

[8] G. J. Harper, *Lancet*, 2: 569, 1943.

TABLE 1

COMPARATIVE IN VITRO RESISTANCE OF STRAINS OF STAPHYLOCOCCI TO PENICILLIN AND POTENCY OF PENICILLIN INHIBITOR PRODUCED BY THESE STRAINS

Strain No.	No. of units of penicillin per ml required to inhibit growth completely	No. of units of penicillin per ml required to inhibit growth completely of sensitive strain of staphylococcus in presence of 0.1 mg per ml of inhibitor
1	20	800*
2	2	60*
3	1	40
4	1	40
5	0.6	30
6	0.6	20
7	0.6	20

* 0.01 mg per ml of inhibitor.

necessary to overcome the inhibitory effect of 0.01 mg per ml of extracted organisms from strain 1. Control observations revealed that only 0.1 unit of penicillin per ml was required to prevent growth of the test strain in the absence of inhibitor. There appears to be a rough correlation between the resistance of a strain to penicillin and the potency of inhibitor produced by that strain.

Another representative group of observations is illustrated in Fig. 1. The effect is shown of 0.005

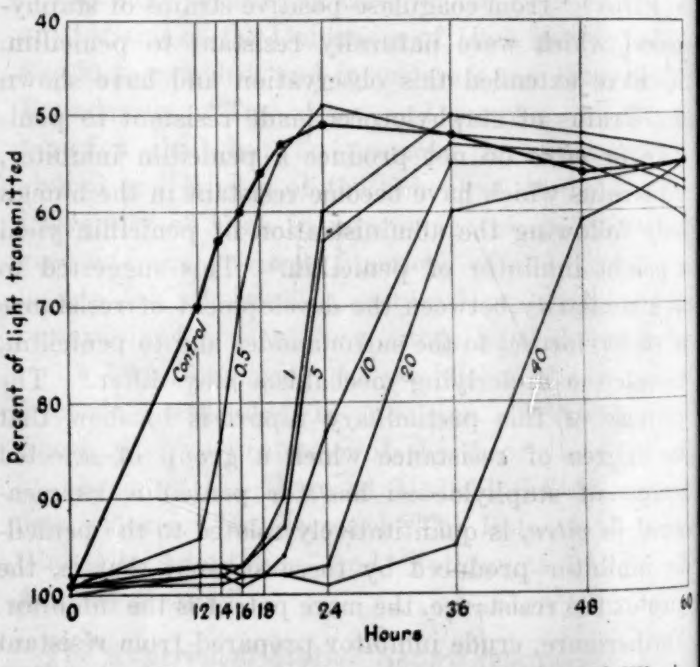

FIG. 1. Effect of 0.005 mgs per ml of penicillin inhibitor upon antistaphylococcic action of sodium penicillin in concentrations varying from 0.5 to 40 units per ml. Turbidity of bacterial growth expressed in per cent. of light transmitted in Evelyn photoelectric colorimeter.

mg per ml of dried bacteria from strain 2 upon the growth curves of a penicillin-sensitive strain of staphylococcus in the presence of varying concentrations of sodium penicillin. The growth of the strain of staphylococcus employed in the tests was inhibited by 0.05 to 0.1 units per ml of penicillin. Although the control tube without penicillin revealed a dense bacterial growth within 24 hours, the inhibitory

effect of penicillin in the other tubes was still being manifested at this time. With the elapse of more time, the inhibitory effect of penicillin was overcome, and the density of growth in all the tubes eventually approximated that of the control tubes.

Using the same penicillin-sensitive strain of staphylococcus, the effect of different amounts of dried bacteria from strain 2 upon the antistaphylococcic action of 1 unit of penicillin per ml was determined. Fig. 2

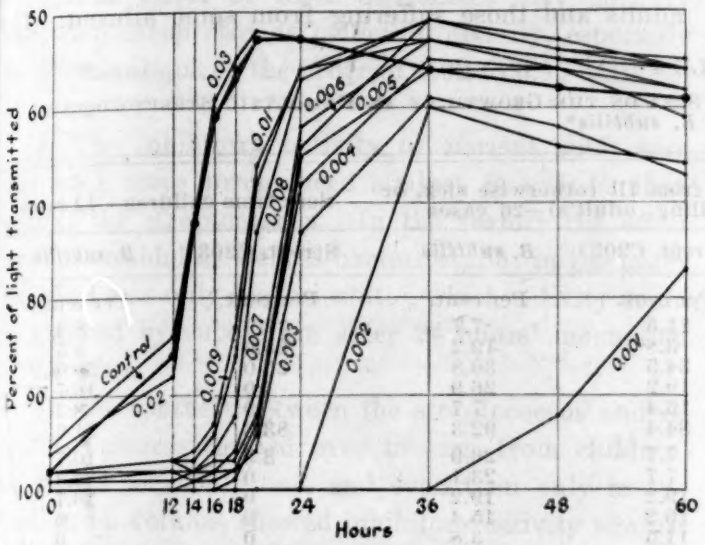

FIG. 2. Effect of concentrations of penicillin inhibitor varying from 0.001 to 0.03 mg per ml upon antistaphylococcic action of 1 unit per ml of sodium penicillin. Turbidity of bacterial growth expressed in per cent. of light transmitted in Evelyn photoelectric colorimeter.

presents the results of one set of growth curves. As the concentration of the penicillin inhibitor increased, a point was reached where the growth of the test strain in the presence of 1 unit of penicillin approximated that of the control tube without penicillin.

It also has been shown that dried bacteria from both penicillin-sensitive and penicillin-resistant strains of staphylococci act as a growth stimulus for coagulase-positive staphylococci when grown in Gladstone's medium.

COMMENT

The foregoing data indicate that one of the mechanisms whereby staphylococci develop resistance to penicillin is the production of a potent inhibitor of penicillin by the organisms. That this is not the only mechanism involved in penicillin-resistance is shown by the fact that staphylococci which have become resistant to penicillin *in vitro* do not yield a demonstrable inhibitor.[5] However, changes in bacterial metabolism are very likely involved in both instances. A feature of the present observations is that an elapse of time is essential for inhibitor from staphylococci to overcome the antibacterial action of penicillin. This time factor is related to both the concentrations of penicillin and to the amounts of inhibitor which are present. With increasing amounts of inhibitor, the antistaphylococcic effect of penicillin is more promptly overcome. Whereas, decreasing quantities of inhibitor require increasing periods of time to inhibit the penicillin. The application of these biologic phenomena to the clinical use of penicillin bear further investigation. Furthermore, the isolation and identification of penicillin inhibitor from staphylococci are desirable from the viewpoint of defining the precise mode of action of penicillin.

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INHIBITING FACTORS IN THE DETERMINATION OF PENICILLIN IN HUMAN SERA

OF the methods proposed for the measurement of penicillin in serum the majority are based on the activity of penicillin on a selected strain of a hemolytic streptococcus.[1-7] A recent publication[8] demonstrated the possible advantages in the use of *B. subtilis* in place of the streptococcal culture (C203) used by most investigators.

Before accepting either method as being superior, and in view of indications of considerable variations in results obtained by the two methods in recent studies on penicillin oral medication in adults,[9] it was decided to determine the extent of the sensitivity of each organism to the inhibitory power of human sera.

The literature on the inhibitory power of blood and serum is considerable. In this respect the work of Tillet[10, 11] is very inclusive. Tillet found that the streptococcidal property of blood from patients suffering from a variety of diseases was pronounced. This property was absent or greatly diminished in the same patients after recovery. Comparative tests with sera from healthy adults showed this activity to be completely absent. Strain susceptibility of hemolytic streptococci varied considerably; one was destroyed by all sera while another by only a few. A third strain was intermediate in sensitivity.

In a study on oral dosage with penicillin,[4] all the determinations of the penicillin concentration in serum were made on sera from children three weeks to twelve years of age. In that study, in agreement with Rammelkamp, the tubes showing no hemolysis, when tested,

[1] C. H. Rammelkamp, *Proc. Soc. Exp. Biol. and Med.*, 51: 95, 1942.
[2] C. Wilson, *Nature*, 152: 475, 1943.
[3] G. Rake and H. Jones, *Proc. Soc. Exp. Biol. and Med.*, 54: 189, 1943.
[4] P. György, *et al.*, *Jour. Am. Med. Asn.*, 127: 639, 1945.
[5] W. M. M. Kirby and L. A. Rantz, *Jour. Bact.*, 48: 603, 1944.
[6] W. McDermott *et al.*, SCIENCE, 101: 228, 1945.
[7] P. Rosenblatt *et al.*, *Jour. Bact.*, 48: 599, 1944.
[8] W. A. Randall *et al.*, SCIENCE, 101: 365, 1945.
[9] P. György *et al.*, to be published.
[10] W. S. Tillet, *Jour. Exp. Med.*, 65: 163, 1937.
[11] W. S. Tillet and C. C. Stock, *Proc. Soc. Exp. Biol. and Med.*, 37: 82, 1937–1938.

proved sterile by subculture on blood agar streak plates.

In eliminating the serum inhibiting factor from streptomycin assays, Stebbins and Robinson[12] have substituted a strain of *Staphylococcus aureus* for *B. subtilis*. This strain of *S. aureus* was included in part of the following series of tests.

EXPERIMENTAL

Sera from three series of persons, with no recent history of penicillin or sulfonamide treatment, were tested for their inhibitory activity on the streptococcal strain C203 by the procedure outlined by György *et al.*[4] The same sera were employed in determining the sensitivity of the strain of *B. subtilis* used in the method proposed by Randall[8] with the exception that the tube dilution system of György's replaced the serial dilution method. Tube dilutions have the advantage of providing closer determinations. The strain of *S. aureus* of Stebbins[12] was eliminated during the investigation for reasons discussed later. However, the test procedure was identical to that used for *B. subtilis*.

The first series consisted of sera from 100 normal adults, kindly supplied by Dr. A. H. Price, of the Jefferson Medical College, Philadelphia, Pa. The second series of 26 sera were obtained through the kindness of Dr. John Sinnott, Jr., of the Pennsylvania Hospital, Philadelphia, Pa., and represent sera from adults suffering from a wide variety of ailments. The sera in the third series, consisting of sera from 12 children, were obtained through the courtesy of Dr. Paul György, of the Department of Pediatrics, University of Pennsylvania School of Medicine.

The second series was included in this work to demonstrate the difference between sera from normal adults and those suffering from some ailment. The series of children was included in order to verify or disprove a contention that sera from children (under 12 years) were not inhibitory to the streptococcal strain C203 to the same degree as were the sera from adults. The contrast in sensitivity between the streptococcal and subtilis cultures was also shown in sera from children.

It has been demonstrated[4] that five minutes in a water bath at 56° C. did not affect the penicillin content of serum. Thus, when sufficient serum was available, 1 ml samples were so treated and any alterations in the inhibitory effect on the two cultures were noted.

Tube results were read after 16 hours, 24 hours and 40 hours of incubation at 37° C. In the initial fifty normal adult sera, subcultures were made on blood agar plates from the tubes showing no visible growth only at the 40-hour period. With the desire to shorten

TABLE 1

THE INHIBITORY AND BACTERICIDAL EFFECT OF HUMAN SERA ON THE GROWTH OF AN HEMOLYTIC STREPTOCOCCUS (C203) AND *B. subtilis**

Tube inhibition at incubation period of	Volume of serum in 2 ml final volume	Normal adult sera—100 cases		Sera from Ill (otherwise sick, or ailing, adult's)—26 cases		Sera from children—12 cases	
		Strept. C203	*B. subtilis*	Strept. C203	*B. subtilis*	Strept. C203	*B. subtilis*
		Per cent.	Per cent.	Per cent.	Per cent.	Per cent.	Per cent.
16 hrs.	1.0 ml	12	18	11.5	7.7	33.3	8.3
	.8 "	18	17	3.8	19.2	25.0	8.3
	.6 "	12	30	34.5	30.8	25.0	50.0
	.4 "	5	21	19.2	26.9	0	16.7
	.2 "	2	3	15.4	7.7	0	8.3
	Total cases	49	89	84.4	92.3	83.3	91.6
24 hrs.	1.0 ml	10	24	7.7	26.9	8.3	16.7
	.8 "	8	23	7.7	23.1	0	33.3
	.6 "	1	18	19.2	19.2	0	16.7
	.4 "	1	6	19.2	15.4	0	0
	.2 "	0	0	11.5	3.8	0	0
	Total cases	20	71	65.3	88.4	8.3	66.7
40 hrs.	1.0 ml	7	29	11.5	26.9	8.3	16.7
	.8 "	5	10	11.5	23.1	0	16.7
	.6 "	1	2	19.2	7.7	0	0
	.4 "	1	1	3.8	3.8	0	0
	.2 "	0	0	7.7	0	0	0
	Total cases	14	42	53.7	61.5	8.3	33.4

Bactericidal activity as demonstrated by absence of growth on subculture	Volume of serum in 2 ml final volume	Normal adult sera—100 cases				Sera from Ill (otherwise sick, or ailing, adult's)—26 cases				Sera from children—12 cases			
		Strept. C203		*B. subtilis*		Strept. C203		*B. subtilis*		Strept. C203		*B. subtilis*	
		24 hrs.†	40 hrs.	24 hrs.	40 hrs.	24 hrs.	40 hrs.	24 hrs.	40 hrs.	24 hrs.	40 hrs.	24 hrs.	40 hrs.
	1.0 ml	0	0	20	18	3.8	3.8	30.7	30.7	8.3	8.3	16.7	8.3
	.8 "	0	1	6	5	15.4	19.3	0	0	0	0	8.3	8.3
	.6 "	0	0	2	1	15.4	11.5	0	0	0	0	8.3	0
	.4 "	0	1	0	0	0	0	3.8	3.8	0	0	0	0
	.2 "	0	0	0	0	7.7	7.7	0	0	0	0	0	0
	Total cases	0	2	28	24	42.3	42.3	34.5	34.5	8.3	8.3	33.3	16.6

* Results are expressed as the per cent. of the total cases showing inhibitory activity at each particular volume of serum. These results, with the exception of the summations, are not cumulative.

† As indicated in the text, the initial 50 normal adult sera were subcultured only at 40 hours, providing a total of 50 cases subcultured at 24 hours and a total of 100 subcultured at 40 hours.

[12] R. B. Stebbins and H. J. Robinson, Merck Institute for Therapeutic Research, Rahway, N. J. Personal communication.

the test duration, subcultures from all remaining sera were made at the 24- and 40-hour periods from tubes showing no visible growth or hemolysis.

RESULTS AND CONCLUSIONS

The results of this investigation, including the data presented in Tables 1 and 2, demonstrate that:

(1) Inhibitory substances to the streptococcal strain C203 and *B. subtilis* exist in human sera.

(2) The effect of these substances may be very easily misinterpreted as penicillin activity, especially in concentrations of the order of 0.02 to 0.05 units/ml of serum.

(3) The inhibitory activity of normal adult sera was much more pronounced against *B. subtilis* than against the streptococcus. In the former the effect was bactericidal as well as bacteriostatic; in the latter the effect was only bacteriostatic, which activity could be nullified by subculture after 24 hours' incubation of the tubes.

(4) The contrast between the streptococcus and *B. subtilis* cultures carried over to sera from children. Of twelve sera only one, and even then only in the 1 ml serum volume, showed inhibitory activity against the streptococcus, whereas bactericidal activity was demonstrated in one third of the sera against *B. subtilis* at 24 hours.

(5) Sera from ailing adults showed pronounced bacteriostatic and bactericidal activity against both microorganisms. This agrees with the observations of Tillet and is probably due to the greater concentration of inhibitory substances whose effect can not be eliminated by subculture.

TABLE 2

THE EFFECT OF HEAT (56° C. WATER BATH FOR 5 MINUTES) ON THE INHIBITORY AND BACTERICIDAL ACTIVITY OF SERA FROM 47 NORMAL ADULTS*

Tube inhibition at incubation period of	Strept. C203		*B. subtilis*	
16 hrs.	27.7 per cent.		55.3 per cent.	
24 "	8.5 " "		48.9 " "	
40 "	4.3 " "		14.9 " "	
Bactericidal activity as demonstrated by absence of growth on subculture at	*24 hrs.*	*40 hrs.*	*24 hrs.*	*40 hrs.*
	0 per cent.	0 per cent.	12.8 per cent.	8.5 per cent.

*1 ml volumes of sera were contained in 2 ml final volumes with broth as diluent. Results are expressed in per cent. of cases showing inhibitory activity as in Table 1

(6) Heating normal adult sera at 56° C. for five minutes lowered the incidence of bacteriostatic activity against the streptococcus and *B. subtilis* but did not eliminate the bactericidal effect against the latter culture.

(7) In the comparison of penicillin dosage forms the streptococcal method, with subculture, has proven of value when sera from children or normal adults are used in such tests.

(8) Neither streptococcal nor *B. subtilis* method are absolutely reliable in the determination of low concentrations of penicillin in ill adults, since neither method can distinguish between penicillin activity and other bacterial inhibitory substances in sera from such individuals.

(9) The sensitivity of a strain of *Staphylococcus aureus*[12] to inhibitory substances in human sera was determined. Although this organism was not inhibited by 1 ml volumes of serum in 50 cases of normal adult serum, because of its insensitivity to penicillin it is not applicable to the determination of low concentrations of penicillin in serum. This organism required 0.08 unit of penicillin per tube for inhibition as compared to 0.02 unit for the streptococcal strain C203.

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CALCIUM CARBONATE AS AN ANTACID FOR ORAL PENICILLIN

EARLY work by Abraham, Florey and associates[1] and Rammelkamp and Keefer[2] indicated penicillin to be ineffective by the oral route because of destruction by stomach acidity. Later, Free *et al.*,[3] using larger doses and more purified penicillin, showed that some penicillin escapes destruction by the stomach acid and is absorbed, thereby renewing interest in the oral route as a possible mode of administration. More recently, somewhat greater absorption has been reported to take place when the penicillin is administered in combination with agents to protect it from destruction by stomach acidity. Libby[4] suspended penicillin in fixed oils and reported a protective effect, but McDermott[5] was not able to show a significant protection by the use of oils. Reports on the administration with certain gastric antacids appear the most favorable. Sodium bicarbonate has been found unsuited for this purpose because of its alkalinity.[1,2,3] Charney *et al.*[6] and Gyorgy *et al.*[7] reported increased absorption by the simultaneous administration of sodium citrate. Sodium phosphate was also

[1] E. P. Abraham, H. W. Florey *et al.*, *Lancet*, 2: 177, 1941.
[2] C. H. Rammelkamp and C. S. Keefer, *Jour. Clin. Invest.*, 22: 425, 1943.
[3] A. H. Free *et al.*, SCIENCE, 100: 431, 1944.
[4] R. L. Libby, SCIENCE, 101: 178, 1945.
[5] W. McDermott *et al.*, SCIENCE, 101: 228, 1945.
[6] J. Charney *et al.*, SCIENCE, 101: 251, 1945.
[7] P. Gyorgy *et al.*, *Jour. Am. Med. Asn.*, 127: 639, 1945.

found to be effective by Charney's group, but aluminum hydroxide or calcium carbonate in milk was not found to be particularly effective. Enteric coating has not given a satisfactory answer to the problem[1, 4, 8] probably due to the variability in the time and location at which the enteric coating disintegrated in the gastro-intestinal tract. Burke *et al.*[9] reported increased absorption by the use of both an enteric coating and aluminum hydroxide as an antacid. It was not determined which of the two factors contributed most to the increase in absorption.

In preliminary experiments with artificial gastric juice *in vitro* and in trials of oral penicillin medication on humans, we also found gastric antacids to be the most promising aid to oral penicillin administration reported up to the present time. It occurred to us that calcium carbonate might be an effective antacid for this purpose because of its very weak alkaline reaction on one hand and its ability to quickly neutralize comparatively large amounts of hydrochloride acid on the other. We reasoned that the milk administered simultaneously with the calcium carbonate and penicillin by Charney's group[6] may have induced a delaying effect on stomach emptying, thereby allowing more time for penicillin destruction in the stomach before its passage into the duodenum for absorption. Therefore, calcium carbonate and five other antacids, including those reported on by other investigators, were studied for comparative effectiveness.

TABLE 1

BLOOD SERUM CONCENTRATIONS OF PENICILLIN FOLLOWING ORAL ADMINISTRATION OF 100,000 UNITS OF CALCIUM SALT WITH VARIOUS ANTACIDS

Antacid	Subject	Serum concentrations of penicillin in units per cc. ½ hr.	1 hr.	2 hr.	3 hr.	4 hr.
Calcium carbonate	1	.312	.624	.312	.156	.078
	2	.312	.039	.019	.019	Trace
	3	.039	.078	.312	.312	.156
	4	.156	.156	.078	.039	.019
	5	...	.312	.078	.039	.039
Average serum concentration		.202	.242	.160	.113	.058
Sodium citrate	6	.039	...	.078	.039	.019
	7	.312	.312	.078	.019	.019
	8	.156	.156	.078	.039	.039
	9	.156	.039	.019	.019	Trace
	10	.156	.156	.039	Trace	Trace
Average serum concentration		.164	.166	.058	.023	.015
Sodium phosphate buffer 12.5% NAH_2PO_4 87.5% Na_2HPO_4 (pH 7.5)	11	.039	.039	.039	.039	Neg.
	12	.039	.039	.039	.039	.039
	13	.039	.039	.078	.039	.019
	14	.039	.039	.039	Trace	Neg.
	15	.156	.078	.039	.039	Trace
Average serum concentration		.062	.047	.047	.031	.012
Aluminum hydroxide	16	.019	.019	.019	.039	.039
	17	.019	.019	.039	.019	.019
	18	.039	Trace	Neg.	Neg.	Neg.
	19	.156	.078	.078	.019	.019
	20	.078	.078	.039	Trace	Trace
Average serum concentration		.062	.039	.035	.015	.015
Magnesium trisilicate	21	.078	.016	Trace	Trace	Trace
	22	Trace	Trace	Trace	Neg.	Neg.
	23	.156	Trace	.019	Trace	Neg.
	24	Trace	.019	.039	.019	Trace
	25	.312	.156	.019	Neg.	Neg.
Average serum concentration		.109	.038	.015	.004	...
Magnesium hydroxide	26	.019	Trace	Trace	Trace	Trace
	27	Trace	Trace	Trace	Neg.	Neg.
	28	Trace	Trace	Trace	Trace	Trace
	29	.019	Trace	Trace	Trace	Trace
	30	.039	Trace	Trace	Trace	Neg.
Average serum concentration		.015	...	...	...	...
No antacid (Penicillin only)	31	.078	.078	.019	.019	.019
	32	.039	.019	Trace	Trace	Trace
	33	.156	.156	.078	.019	Trace
	34	.039	.156	.156	.078	.078
	35	.156	.156	.039	Trace	Trace
Average serum concentration		.094	.113	.058	.023	.019

All penicillin-antacid combinations were mixed in the dry state and administered in gelatin capsules with a glassful of water to fasting human subjects. The dose of penicillin used was 100,000 units calcium penicillin combined with 2 grams of the antacid being studied. This dose of antacid was arbitrarily selected as an average therapeutic dose and one which could be conveniently administered in tablet or capsule form. Each penicillin antacid combination was administered to a group of five subjects. The same dose of penicillin with no antacid was also administered to a control group. Blood samples were drawn at intervals up to four hours after administration and the serum was assayed for penicillin by the method of Rammelkamp.[10]

COMMENTS

The average serum levels following the administration of 100,000 units calcium penicillin with 2 grams of calcium carbonate are approximately twice as high at all test periods as the average serum levels following the administration of 100,000 units of calcium penicillin alone. The average serum levels obtained with the penicillin-sodium citrate combination are also generally higher than those obtained by the administration of penicillin alone, which is in accord with the work of Gyorgy.[7] The average serum levels obtained following the administration of penicillin with dry sodium phosphate buffer, aluminum hydroxide, magnesium trisilicate or magnesium hydroxide are all inferior to those obtained by the administration of penicillin alone. Therefore, the latter compounds in the dry form do not appear to be indicated as an aid to the oral administration of penicillin.

Calcium carbonate is classified as a non-systemic

[8] M. E. Florey and H. W. Florey, *Lancet*, 1: 387, 1943.

[9] F. G. Burke *et al.*, *Jour. Am. Med. Asn.*, 128: 83, 1945.

[10] C. H. Rammelkamp, *Proc. Soc. Exp. Biol. and Med.*, 51: 95, 1942.

antacid because of the insoluble and non-absorbed calcium compounds reformed in the intestinal tract after the passage of the chloride from the stomach.[11] It may therefore prove to be a safer antacid to administer repeatedly with penicillin than a soluble buffer salt such as sodium citrate, which is a systemic antacid and can lead to alkalosis. Dosage schedules for the maintenance of therapeutic blood levels by the oral administration of penicillin with calcium carbonate are being investigated.

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SYNTHESIS OF A COMPOUND IDENTICAL WITH THE L. CASEI FACTOR ISOLATED FROM LIVER[1]

PREVIOUS work has indicated the existence of a new growth factor(s) essential for the growth of *Lactobacillus casei* and *S. faecalis* R and necessary for growth and hemoglobin formation in the chick. These fractions or compounds have been variously designated as the norite eluate factor,[2,3] folic acid,[4] vitamin Bc,[5] *L. casei* factor from liver[6] and *L. casei* factor from a fermentation residue.[7] We wish to report the synthesis of a compound which is identical with the *L. casei* factor isolated from liver. The synthetic compound is active for *L. casei*, *S. faecalis* R and is effective in promoting growth and hemoglobin formation in the chick.

The identity of the synthetic compound and the *L. casei* factor isolated from liver is based on the following observations. The ultraviolet absorption spectra of the synthetic and natural compounds are identical. The $E^{1\%}_{1\ cm}$ values for the two compounds are shown in Table 1.

The infra-red spectra of the synthetic and natural compound were determined and compared by Dr. R. C. Gore, of the Stamford Research Laboratories, American Cyanamid Company. The per cent. transmission of the two compounds is given in Fig. 1. Dr. Gore states, "With correspondence in absorption exhibited at so many frequencies the probability is extremely high that the two molecules are identical."

TABLE 1

ULTRAVIOLET ABSORPTION SPECTRA OF NATURAL AND SYNTHETIC L. CASEI FACTOR

Solvent		mμ	*L. casei* factor from liver $E^{1\%}_{1\ cm}$	Synthetic *L. casei* factor $E^{1\%}_{1\ cm}$
0.1 N NaOH	Minima	235	287	290
	Maxima	256	565	570
	Minima	268	485	495
	Maxima	283	550	560
	Minima	332	133	135
	Maxima	365	195	199
0.1 N HCl	Minima	262	253	265
	Maxima	296	440	445

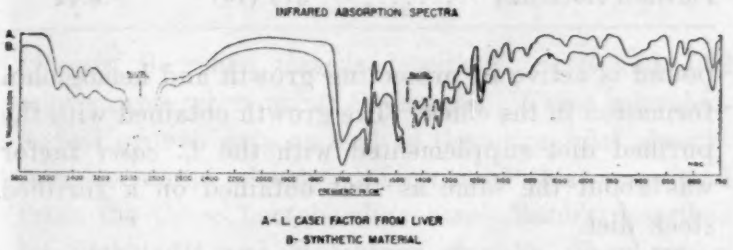

FIG. 1. Infrared absorption spectra of natural and synthetic *L. casei* factors.

Microscopical examination of the natural and synthetic compound was performed by Dr. A. F. Kirkpatrick, of the Stamford Research Laboratories, American Cyanamid Company. Dr. Kirkpatrick reported:

> The compounds which were crystallized as the free acids formed thin lenticular crystals, exhibiting birefringence and parallel extinction. The refractive index for light vibrating parallel to the length of the crystals was 1.559 ± 0.003 for the natural compound and 1.559 ± 0.003 for the synthetic compound; the refractive index for light vibrating parallel to the width was 1.744 ± 0.003 for the natural product and 1.744 ± 0.003 for the synthetic compound.

The natural and synthetic compounds were equally active when assayed by *L. casei* or *S. faecalis* R. The amount required per ml of medium for half-maximum growth of *L. casei* was 0.00007 micrograms for the natural and 0.00007 micrograms for the synthetic compound. For *S. faecalis* R the amount required per ml for half-maximum growth was 0.0003 micrograms for the natural and 0.0003 micrograms for the synthetic compound. The amounts required for half-maximum growth are slightly greater than previously reported, but the amount required to produce half-maximum growth varies somewhat with different experiments.

[11] L. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Company, 1941.

[1] The announcement of the synthesis of this compound and its availability for experimental use was made at Gibson Island, Maryland, July 18, 1945.

[2] E. E. Snell and W. H. Peterson, *Jour. Bact.*, 39: 273, 1940.

[3] B. L. Hutchings, N. Bohonos and W. H. Peterson, *Jour. Biol. Chem.*, 141: 521, 1941.

[4] H. K. Mitchell, E. E. Snell and R. J. Williams, *Jour. Am. Chem. Soc.*, 63: 2284, 1941.

[5] J. J. Pfiffner, S. B. Binkley, E. S. Bloom, R. A. Brown, O. D. Bird, A. D. Emmett, A. G. Hogan and B. L. O'Dell, SCIENCE, 97: 404, 1943.

[6] E. L. R. Stokstad, *Jour. Biol. Chem.*, 149: 573, 1943.

[7] B. L. Hutchings, E. L. R. Stokstad, N. Bohonos and N. H. Slobodkin, SCIENCE, 99: 371, 1944.

The synthetic compound was assayed with chicks and found to be active. Day-old New Hampshire Red chicks in groups of ten were placed on a purified ration[8] supplemented with varying amounts of the synthetic compound. The positive control diet consisted of commercial chick-starting mash fortified with 3 per cent. cerophyl, 3 per cent. dried liver cake and 2 per cent. yeast. The responses are tabulated in Table 2. These results show that the synthetic compound is active in promoting growth and hemoglobin formation in the chick. The growth obtained with the purified diet supplemented with the *L. casei* factor was about the same as that obtained on a fortified stock diet.

TABLE 2

EFFECT OF SYNTHETIC L. CASEI FACTOR ON GROWTH AND HEMOGLOBIN FORMATION IN THE CHICK

Supplements per kg ration	Average weight and number alive (–) at 28 days	Average hemoglobin gm per cent. at 28 days
None	93 (5)	4.40
0.5 mg synthetic compound	306 (9)	7.80
1.0 mg synthetic compound	304 (9)	7.36
Fortified stock diet	319 (10)	6.44

From the data presented it is evident that the synthetic compound is identical with the natural *L. casei* factor isolated from liver.

Details of the isolation, degradation and synthesis will be subjects of subsequent communications.

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[8] B. L. Hutchings, E. L. R. Stokstad, N. Bohonos, J. J. Oleson and L. W. McElroy. Paper presented April 5, 1944, at the Cleveland meetings of the American Chemical Society.

ISOLATION OF AN ANTIANEMIA FACTOR (VITAMIN Bc CONJUGATE) IN CRYSTALLINE FORM FROM YEAST

THE constituents of yeast which are active in preventing nutritional anemia have been of particular interest since Wills[1] in 1931 demonstrated the curative effect of yeast extract in the macrocytic anemia of pregnancy which occurs commonly in India. She and Bilimoria[2] found that monkeys developed an anemia, leucopenia and granulocytopenia on a diet comparable to that consumed by the natives. These and other symptoms were relieved by yeast extract. Day and his co-workers[3] devised a different type of diet for monkeys on which the animals developed a similar syndrome. They were able to correct or prevent the deficiency state with yeast and suggested that the monkey factor be called vitamin M.[4] According to Day[5] it required about a year to evaluate the potency of a material by studies on monkeys. Later Hogan and Parrott[6] observed that chicks develop an anemia under defined dietary conditions which could be cured with liver extracts and they named the chick factor vitamin Bc. Their observations on chicks made available a convenient animal assay method for at least one antianemia factor and we initiated studies on the concentration of the chick antianemia factor in yeast in 1941. It was apparent early in our work that the chick antianemia factor in yeast differed chemically from vitamin Bc in liver extracts. Meanwhile Mills *et al.*[7] suggested that the microbiological growth factor in liver ("norite eluate factor" of Snell and Peterson[8]) and the chick antianemia factor in liver extracts may be identical. Use of both microbiological and chick assay methods soon led us to the isolation from liver of a crystalline compound having both activities. This compound we called tentatively vitamin Bc.[9] However, concentrates from yeast rich in chick antianemia activity were found to have very little microbiological growth activity for *L. casei* or *S. faecalis*, and we showed that crystalline vitamin Bc

[1] L. Wills, *Brit. Med. Jour.*, 1: 1059, 1931.
[2] L. Wills and H. S. Bilimoria, *Indian Jour. Med. Research*, 20: 391, 1932.
[3] P. L. Day, W. C. Langston and C. F. Shukers, *Jour. Nutrition*, 9: 637, 1935.
[4] P. L. Day, W. C. Langston and W. J. Darby, *Proc. Soc. Expt. Biol. and Med.*, 38: 860, 1938.
[5] P. L. Day, in "Vitamins and Hormones," edited by R. S. Harris and K. V. Thimann, Acad. Press Inc., New York, 1944, Vol. 2, p. 99.
[6] A. G. Hogan and E. M. Parrott, *Jour. Biol. Chem.*, 132: 507, 1940; 128: Proc. xlvi, 1939.
[7] R. C. Mills, G. M. Briggs, Jr., C. A. Elvehjem and E. B. Hart, *Proc. Soc. Exp. Biol. and Med.*, 49: 186, 1942.
[8] E. E. Snell and W. H. Peterson, *Jour. Bact.*, 39: 273, 1940.
[9] J. J. Pfiffner, S. B. Binkley, E. S. Bloom, R. A. Brown, O. D. Bird, A. D. Emmett, A. G. Hogan and B. L. O'Dell, SCIENCE, 97: 404, 1943.

could be isolated from such concentrates following digestion with suitable enzyme preparations.[10] In view of these results we referred to the chick antianemia factor in yeast as vitamin Bc conjugate and the enzyme which formed vitamin Bc from it, vitamin Bc conjugase.[11] On the basis of these observations we devised an enzymatic-microbiological method of assay for vitamin Bc conjugate.[12]

Using the enzymatic-microbiological assay method in conjunction with chick anemia methods of assay we have recently isolated a crystalline compound from yeast which by its properties we judge to be the substance to which we referred earlier as vitamin Bc conjugate. The compound crystallizes from 5 per cent. sodium chloride solution in the form of yellow birefringent microcrystalline spherulites and on repeated recrystallization as rosettes of microcrystalline needles. It has no melting point. When heated on the hot stage it begins to darken from about 200° C. and partially melts at 230–260° C., but the charred mass never becomes entirely molten up to 360° C. A specimen containing 2.56 per cent. ash (sodium chloride) had the following corrected elementary composition: C 49.61 per cent.; H 5.36 per cent.; N 14.79 per cent. Phosphorus and sulfur were absent. The compound yields a crystalline methyl ester which melts with decomposition at 212–215° C. (corr.). The melting range of the methyl ester is reproducible but depends to a considerable extent on the size of the crystalline aggregate being observed and the rate of heating. The following analytical values were obtained on an ash-free sample of the crystalline ester: C 50.94, 50.91 per cent.; H 6.04, 6.10 per cent.; N 14.20 per cent.

The specific ultraviolet absorption properties of the compound are compared with those of vitamin Bc in Fig. 1.[13] The shapes of the curves are almost identical, differing only in the $E^{1\%}_{1\ cm}$ values indicating that both substances have the same chromophoric groups. It appears from these data that the molecular size of this yeast antianemia factor is 2.8 times that of vitamin Bc. From the elementary composition it follows that the non-vitamin Bc portion of the molecule contains nitrogen.

The new crystalline product is only slightly stimulating to the growth of *L. casei* or *S. faecalis*. One microgram is equivalent to .003–.006 micrograms of

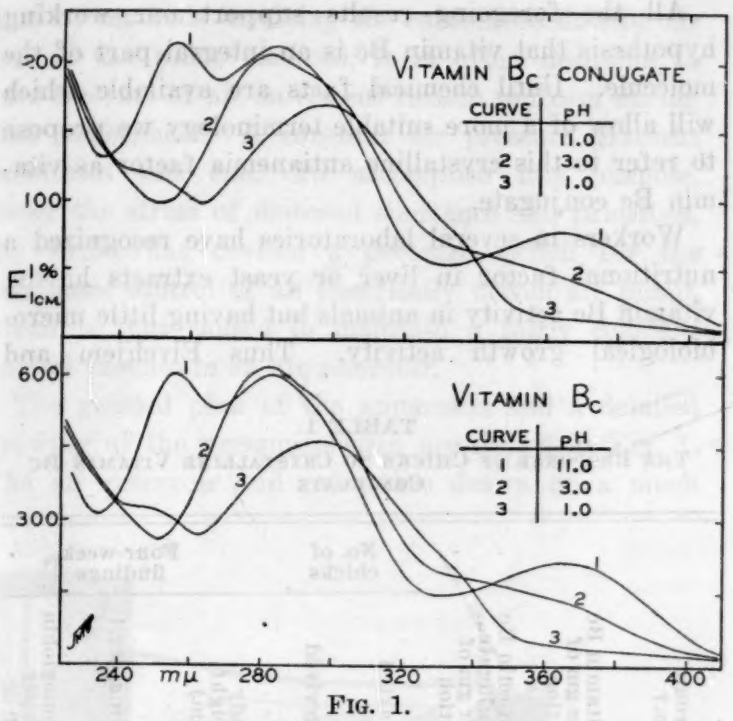

FIG. 1.

vitamin Bc when measured with *L. casei* and .002 micrograms when using *S. faecalis*. These microbiological growth data as well as the ultraviolet absorption constants clearly differentiate this compound from the three *Lactobacillus casei factors* described by Stokstad[14] and Hutchings *et al.*[15] They report that all three of their compounds, including their *new Lactobacillus casei factor* obtained from an undisclosed source, are powerful growth factors for *L. casei*.[15]

Vitamin Bc conjugase from hog kidney releases an amount of vitamin Bc from the crystalline compound approximating that present in conjugated form as calculated from the ultraviolet absorption data in Fig. 1. The amount of vitamin Bc in the digestion mixtures was estimated by microbiological assay using *L. casei* and *S. faecalis*. It should be pointed out that the enzymic degradation of the conjugate is not an entirely reliable reaction. The endpoint under presumably identical conditions may vary appreciably. The enzyme does not attack the methyl ester but degrades the regenerated parent compound. Hence there must be at least one free carboxyl group in the conjugate molecule in order for the compound to serve as a substrate for vitamin Bc conjugase.

The antianemic and growth effects of the new crystalline compound were compared in the chick with those of crystalline vitamin Bc. The results are summarized in Table 1. The data demonstrate that the vitamin Bc present in the conjugate molecule as calculated from ultraviolet absorption data and as found by enzymatic microbiological assay is available to the chick.

[10] S. B. Binkley, O. D. Bird, E. S. Bloom, R. A. Brown, D. G. Calkins, C. J. Campbell, A. D. Emmett and J. J. Pfiffner, SCIENCE, 100: 36, 1944.

[11] O. D. Bird, S. B. Binkley, E. S. Bloom, A. D. Emmett and J. J. Pfiffner, *Jour. Biol. Chem.*, 157: 413, 1945.

[12] O. D. Bird, Betty Bressler, R. A. Brown, C. J. Campbell and A. D. Emmett, *Jour. Biol. Chem.* In press.

[13] We wish to thank Dr. J. M. Vandenbelt for the ultraviolet absorption measurements and the preparation of the chart.

[14] E. L. R. Stokstad, *Jour. Biol. Chem.*, 149: 573, 1943.

[15] B. L. Hutchings, E. L. R. Stokstad, N. Bohonos and N. H. Slobodkin, SCIENCE, 99: 371, 1944.

All the foregoing results support our working hypothesis that vitamin Bc is an integral part of the molecule. Until chemical facts are available which will allow of a more suitable terminology we propose to refer to this crystalline antianemia factor as vitamin Bc conjugate.

Workers in several laboratories have recognized a nutritional factor in liver or yeast extracts having vitamin Bc activity in animals but having little microbiological growth activity. Thus Elvehjem and associates[16] have prepared liver fractions having antianemia activity in the chick but having little microbiological growth activity for *L. casei* or *S. faecalis*. They postulated the existence of two new vitamins in these fractions, vitamins B_{10} and B_{11}. Day and his coworkers[17] have recognized the existence in yeast of a "potential *S. lactis* R stimulating factor" which could be converted to an "*S. lactis* R stimulating factor" by an enzyme in liver and other organs. They found that extracts rich in vitamin M activity had a high content of "potential *S. lactis* R stimulating factor" and recently suggested the possible identity of vitamin M, vitamin Bc conjugate and the "potential *S. lactis* R stimulating factor."[18] Welch and Wright[19] and Wright *et al.*[20] recognized a "potential folic acid" in milk powder, and Sebrell[21] noted the existence of a factor in yeast which had little "folic acid" activity but which was active in correcting the anemia of rats on a succinylsulfathiazole diet. Hill, Norris and Heuser[22] have recently found their yeast factors R and S to be associated with antianemia activity in the chick but not with microbiological growth activity. Factor R was thought to be identical with the chick growth factor U of Stokstad and Manning.[23] It appears probable that further study will demonstrate the identity of a number of these factors, including the yeast human nutritional factor of Wills with the crystalline compound described herein.

TABLE 1

THE RESPONSE OF CHICKS TO CRYSTALLINE VITAMIN Bc CONJUGATE

Group No.†	Vitamin Bc per gm of ration	Vitamin Bc conjugate per gm of ration	No. of chicks: Started	No. of chicks: Survived	Four-week findings: Body weight (gm)	Four-week findings: Hematocrit	Four-week findings: Hemoglobin gm per 100 cc
	(mcg.)	(mcg.)					
1	0	0	10	5	126	15.4	3.73
2	0.05*	0.14	10	7	122	17.1	4.58
3	0.15*	0.42	9	9	166	24.0	7.01
4	0.25*	0.70	9	8	198	27.0	8.34
5	2.00*	5.60	5	5	202	30.8	9.53
6	0.05	0	9	7	134	15.6	4.53
7	0.15	0	10	10	175	28.4	8.27
8	0.25	0	10	10	240	29.3	8.78
9	2.00	0	5	5	221	30.8	9.45

† The conditions for the prophylactic assay were those described by C. J. Campbell, R. A. Brown and A. D. Emmett, *Jour. Biol. Chem.*, 152: 483, 1944.

* As estimated from the specific ultraviolet absorption properties of crystalline vitamin Bc conjugate.

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SCIENTIFIC APPARATUS AND LABORATORY METHODS

THE EFFECT OF SPECIFIC AMINO ACIDS ON THE YIELD OF PENICILLIN IN SUBMERGED CULTURE[1]

IN the course of a survey of media to substitute for corn-steep liquor in the production of penicillin by deep culture the basic nutrition of *Penicillium notatum No. 832* was investigated. When it was found that wheat extracts or "stillage" from alcoholic fermentation of wheat could serve as suitable media, these were fractionated and the fractions tested to identify the nature of the stimulus to growth of the mold and the production of penicillin. At the same time fractions of tryptic or acid hydrolysates of pure

[16] G. M. Briggs, Jr., T. D. Luckey, C. A. Elvehjem and E. B. Hart, *Jour. Biol. Chem.*, 148: 163, 1943; *ibid.*, 158: 303, 1945.

[17] V. Mims, J. R. Totter and P. L. Day, *Jour. Biol. Chem.*, 155: 401, 1944.

[18] M. E. Mallory, V. Mims, J. R. Totter and P. L. Day, *Jour. Biol. Chem.*, 156: 317, 1944.

[19] A. D. Welch and L. D. Wright, SCIENCE, 100: 154, 1944.

[20] L. D. Wright, H. R. Skeggs, A. D. Welch, K. L. Sprague and P. A. Mattis, *Jour. Nutrition*, 29: 289, 1945.

[21] W. H. Sebrell, Harvey Lectures, 39: 288, 1943–44.

[22] F. W. Hill, L. C. Norris and G. F. Heuser, *Jour. Nutrition*, 28: 175 (1944).

[23] E. L. R. Stokstad and P. D. V. Manning, *Jour. Biol. Chem.*, 125: 687 (1938); E. L. R. Stokstad, P. D. V. Manning and R. E. Rogers, *Jour. Biol. Chem.*, 132: 463 (1940).

[1] With financial assistance from the National Research Council of Canada.

proteins were also tested in deep culture and found to be active.

In each instance stimulation of growth and production of penicillin was obtained with the butyl alcohol soluble fraction. This was attributed to proline or hydroxyproline, and tests in deep culture with continuous shaking showed that pure proline was active but hydroxyproline was inactive.

A straight line relationship existed between the concentration of proline and the yield of mycelium in a basal media containing Czapek-Dox minerals and 4 per cent. lactose. The penicillin assays increased with the yield of mycelium but the yields of penicillin were low as compared to corn-steep liquor.

Other amino acids were investigated separately and in combination with proline. Glutamic acid with proline increased the yield of penicillin, *e.g.*, Czapek-Dox salt solution plus 4 per cent. lactose, 0.1 per cent. proline and 0.1 per cent. glutamic acid, inoculated with spores of the mold and agitated in a shaker, gave a yield of 35 Oxford units of penicillin per cc. Aspartic acid could substitute for glutamic acid. Histidine, methionine, tryptophane, hydroxyproline and phenylalanine had no effect. The addition of arginine to proline had a slight stimulatory effect. A summary of the more significant results is given in Table 1.

TABLE 1

	Age of culture (days)	Wt. of mycelium (gm)	Yield of penicillin (Oxford units per cc)*
Czapek-Dox + 4% lactose	7	0.019	0
	10	....	0–0.1
Czapek-Dox + 4% lactose, + 0.2% proline	7	0.290	4–6
	10	....	9–11
Czapek-Dox + 4% lactose, + 0.2% proline + 0.2% glutamic acid	7	0.358	17–21
	10	....	32–36

* Range of values in triplicate tests. Yields confirmed by extracting the penicillin from the acidified crude medium with amyl acetate and reextracting from amyl acetate into buffer solution at pH 7 which was then re-essayed.

It is interesting to note that proline and glutamic acid are the amino acids present in the highest concentration in wheat and corn proteins. Details of this research will be published elsewhere.

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AUTOMATIC ELECTRIC SWITCH FOR CONSTANT AIR PRESSURE

In the measurement of such physiological processes as respiration, photosynthesis and transpiration, by methods involving the continuous flow of air around the plant material, it is often desirable to have the rate of air movement remain uniform during each experiment. A constant air pressure gradient facilitates this end. To accomplish this purpose, under the stress of material shortages and priorities, the writer has devised a pressure switch for the automatic control of an electrically driven air pump, which is thus caused to maintain a fairly constant partial vacuum in an air reservoir.

The general plan of the apparatus and a detailed drawing of the pressure switch are shown in Fig. 1. The air reservoir and pump are drawn on a much

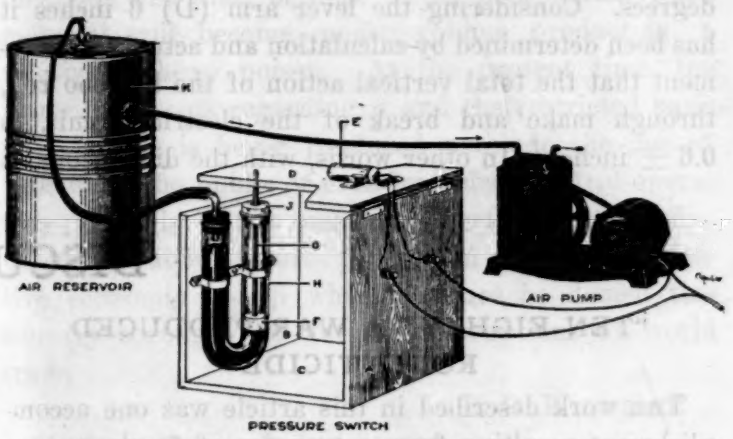

FIG. 1. Automatic pressure switch. Description in text.

smaller scale than the pressure switch. The pressure switch is designed to operate a rocker-type mercury electric switch (E) of suitable capacity. A switch (Central Scientific Co., number 84350C), having a rating of 220V and 1000W, has been quite satisfactory. This mercury switch will make and break contact when tilted through an angle of 3.5 degrees. It is mounted upon a light weight board (D) which is further trimmed to reduce its weight. This board is fastened at one end by hinges to the vertical board (A). The free end of the board (D) rests upon the upper end of a light bamboo rod (G) which passes through a loose-fitting hole in a cork stopper (J) into a cork float (F). The float rides upon the surface of the mercury in one arm of the glass U-tube (H). The bore of the U-tube is 3 cm, but this dimension may be varied, as required, to accommodate a float of sufficient buoyancy to support board (D). The arms of the U-tube are 6 inches in length, which allows for a maximum of about 5 inches, in mercury, of air pressure deficit (suction) in the air reservoir. Values less than 5 inches may be obtained by shortening rod (G). To obtain a larger air pressure deficit would only necessitate using a U-tube with longer arms and increasing the lengths of the vertical supports (A, B) and the bamboo rod (G) proportionately. The length of the bamboo rod is adjusted, by cutting off the top

end, so that contact in the mercury switch is broken with the desired amount of depression of mercury in the float containing arm of the U-tube.

The lengths of the uprights (A and B) are 7.5 inches and 6.5 inches, respectively. Board (A) needs to be slightly longer than (B) to allow for the lever action of (D). The length of board (C) is 6.5 inches, which makes the horizontal distance between (A) and the bamboo rod 6 inches. This latter distance is critical, as it determines the amount of rise and fall of the bamboo rod hence fluctuation in air pressure, required to make and break the electric circuit in (E). As stated above, this mercury switch will make and break contact when tilted through an angle of 3.5 degrees. Considering the lever arm (D) 6 inches it has been determined by calculation and actual measurement that the total vertical action of the bamboo rod, through make and break of the electric circuit, is 0.6 ± inches. In other words, with the dimensions as given the mercury level fluctuates up and down over a distance of 0.6 ± inches with each cycle of start and stop of the electric air pump. If less variation in pressure in the air reservoir is desired one needs only to move (A) and (B) closer together by shortening (C).

A steel drum is being used as the air reservoir. The air pressure in the reservoir is maintained at a deficit with respect to the atmosphere, by an air pump whose operation is controlled by the automatic pressure switch. A wide-mouth glass bottle of 5-gallon size would probably be quite as satisfactory as the steel drum. A large rubber stopper (K) in the air reservoir is fitted with glass tubes. One of these tubes is connected to the air pump, while the others are connected with absorption towers or other gas analyzing devices as desired.

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DISCUSSION

"TEN-EIGHTY," A WAR-PRODUCED RODENTICIDE

THE work described in this article was one accomplishment resulting from a transfer of funds, recommended by the Committee on Medical Research from the Office of Scientific Research and Development to the Fish and Wildlife Service of the Department of the Interior. Administration of this project and the studies connected with it were conducted by the Wildlife Research Laboratory in Denver as part of its long-established search for new rodenticides. It was aided greatly by chemists at the Economic Investigations Laboratory at the Patuxent Research Refuge in Maryland. During the biennium following the grant of funds more than a thousand substances, largely synthetic in origin, were prepared or obtained from cooperators and bioassayed at the Patuxent Laboratory and the more toxic ones subjected to confirmatory tests at the Denver laboratory.

Initial experimentation was carried out with albino rats, but in view of the inherent limitations in the use of these animals in solving problems associated with wild creatures, the later tests were conducted with captive wild Norway rats, prairie dogs and other field rodents in the control of which the new rodenticides eventually would be used. Subsequent to the laboratory work with caged animals the more promising materials were tested under actual field conditions.

Several potentially effective rodenticides have been disclosed in the course of this work. One, commonly referred to under its laboratory serial number, "1080," but chemically designated as sodium fluoroacetate, has been subjected to sufficiently adequate field testing to warrant the assertion that a promising new rodenticide has been discovered. Although its toxicity to laboratory animals had been known for some time, knowledge of its utility as a practical rodenticide now rests largely on the work to which reference is here made.

Compound "1080" is extremely toxic to a variety of small mammals, a fact which has called for the utmost caution in handling it because of its potential hazard to human beings, domestic livestock and beneficial wildlife that might accidentally come in contact with it. The following approximately LD50 per cent doses for "1080" when administered in food baits have been determined by those engaged in this study:

Leghorn hens	10.00 mg/kg
Deer mice (*Peromyscus*)	5.0 mg/kg
Wood rat (*Neotoma*)	5.0 mg/kg
Wild Norway rats (*R. norvegicus*)	5.0 mg/kg
Tame white rats	2.5 mg/kg
Black-tailed prairie dogs (*C. ludovicianus*)	2.5 mg/kg
Meadow mice (*Microtus*)	0.5 mg/kg
Domestic dogs	0.35 mg/kg
Fisher's ground squirrel (*C. beecheyi fisheri*)	0.35 mg/kg
Wild black rats (*R. rattus* subsp.)	0.1 mg/kg

In addition to its high toxicity to small mammals several of the other characteristics of "1080" have a bearing on its ultimate utility as an effective and usable rodenticide. It is very soluble in water, and when this factor is combined with its high toxicity the very dilute solutions needed reduce to a minimum any objectionable tastes that might lessen acceptance by rodents. Early tests have shown that there is no significant difference in its toxicity with respect to the

exes of laboratory animals. There is, however, indication that laboratory rats acquire a tolerance to "1080" by the ingestion of sublethal doses over a period of from 5 to 14 days. This factor might lower effectiveness of this poison when premises are reated after a short interval of time, but cessation f dosing for a period of 7 days caused laboratory ats to lose this tolerance.

Caged wild Norway and black rats also developed gradually increasing aversion to the material when ffered as water-solutions, but here again this aversion was not sufficiently pronounced to disrupt actual perational procedures. As a matter of fact this aterial exposed as a water solution has given results n rat control in Southern States seldom if ever atched in thoroughness by previously used poisons r other control methods. Similarly effective control as been recorded when the material has been used on rain baits against such field rodents as Beechey's and isher's ground squirrels in California, Richardson's round squirrels in South Dakota, black-tailed, Gunison and Zuni prairie dogs in Colorado, and the orway, black, Alexandrine and frugivorous rats, as ell as the house mouse, in the South.

With a material as new as "1080" much remains be learned regarding its worth and hazards. Little known of its effect on creatures other than those is aimed to control. Its high toxicity to domestic ogs and cats precludes its use where those pets have ree range, and by inference one must conclude its ction will be severe on beneficial wild predators and ur bearers were the material ill-advisedly exposed. f still greater importance is the possible danger to perators who may use it carelessly, no effective antiotes having yet been developed.

It is therefore more as an expression of caution nd withheld judgment than of an announcement of ccomplished fact that this statement has been preared. Research personnel of the Fish and Wildlife ervice to whom major credit should be given for he development and demonstration of the effectiveess of "1080" are continuing their studies in colaboration with various other Federal, State and local gencies and the Armed Services here and abroad to he end that the action of this material may have the ullest scrutiny before it is adopted for widespread se.

In conclusion it seems eminently fitting that recogition for the obtaining and "screening" of "1080" rom a multitude of other potential rodenticides being one under contract from the O.S.R.D. should be iven to Dr. Ray Treichler of the Economic Investiations Laboratory at the Patuxent. Further demontration of toxicity to caged wild rodents and the mmediate direction of the "search for new rodenticides" project of the Fish and Wildlife Service, of which the O.S.R.D. contract has become a part, has been an accomplishment of Justus C. Ward of the Denver Laboratory. To D. A. Spencer of the same staff goes credit for able demonstration of the utility of the material against western field rodents, and the organization of field tests generally, while H. J. Spencer, a field representative of the laboratory, is in large part responsible for the development of this poison in water solutions as a raticide in typhus areas of the South.

The manufacture of "1080" is still on a limited scale and for the experimental work under way. Indications are that, because of its high toxicity, the material will become, under volume production, a relatively cheap poison. At the present time, the many unknowns regarding it and the restricted basis on which it is being produced preclude the use of "1080" by the public or even by rodent control operators generally. It is reasonably certain that the discovery of "1080" assures this nation of a highly effective economic poison which can not be denied this country through any future interruptions of world trade.

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PECTIN INTRAVENOUSLY

IN a recent paper, Baier, Bryant, Joseph and Palmer[1] stated that intravenously injected pectin is not accumulated in the liver as it is easily hydrolyzable and thus differs fundamentally from other plasma substitutes, such as acacia. Previous studies of Hueper[2] and Popper, Volk, Meyer, Kozoll and Steigmann,[3] however, have unequivocally shown that pectin, even when partly degraded, is apparently retained in various organs (liver, kidney, bone marrow, spleen, arteries) and gives rise here to foam cellular formations, hyaline necroses, foreign body giant cells and calcium incrustations. Such observations have been made in experimental animals as well as in men to whom pectin solutions were given for therapeutic reasons. Intravenously injected pectin is therefore not as harmless and fundamentally superior to other macro-molecular colloidal plasma substitutes as this may appear from the statement of Baier, Bryant, Joseph and Palmer.

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[1] W. E. Baier, E. F. Bryant, G. H. Joseph and G. H. Palmer, SCIENCE, 101: 670, 1945.
[2] W. C. Hueper, *Arch. Path.*, 34: 883, 1942.
[3] H. Popper, B. Volk, D. D. Meyer and Fr. Steigmann, *Arch. Surg.*, 50: 34, 1945.

"ISOSENSITIVITY" INSTEAD OF "ISOIMMUNITY"

RECENT progress in the discovery and elucidation of immunologic differences in human blood has been materially aided by the prompt acceptance of new terms which it has been necessary to introduce. Those who would learn of the complicated inter-relationships of the Rh types of human blood and their clinical implications have thus been spared the confusion which would accompany the mastery of several synonyms to designate each new phenomenon. It is with reluctance, therefore, that I propose the replacement of a term which has already gained considerable usage.

The word "isoimmunity" has been employed to denote the development in man of antibodies which act against the agglutinogens in the erythrocytes of another person as a result of previous contact with the antigenic substances in the red cells, either by repeated transfusions or by pregnancy. The prefix *iso-* has been accepted in this field to imply derivation from the same species. Immunologists have construed the word "immunity" to include any state in which antibodies have been developed as the result of exposure to antigens, regardless of whether the condition affords protection to the body or not. This represents an extension of the original meaning of the English word, which still carries with it, in non-technical language, the implication of protection, whereas "isoimmunity" is intended to apply to a state of vulnerability caused by the development of antibodies.

Experience in teaching medical students and physicians about isoimmunity has impressed me with the fact that this term is the source of much confusion because the false implication of protection still persists in the minds of some. I propose to substitute for "isoimmunity" the synonym "isosensitivity," and, for "isoimmunization," the term "isosensitization." The meaning of vulnerability is unmistakably conveyed to the clinician who is already familiar with the terms "sensitivity" and "sensitization" in the field of allergy and has no doubt about their significance to the patients.

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THE GULF HAMMOCK FORMATION IN FLORIDA

FOR a long time it has been an axiom of Florida geology that nowhere within the State is there exposed any formation older than the Ocala limestone. Now it seems that this axiom, like so many others, must be abandoned.

Until recently the Avon Park formation[1] which directly underlies the Ocala limestone, has been known only from core borings and well cuttings, excellent material for work on the microfauna but of little or no value in studying the larger fossils. A short time ago the writer was lucky enough to find a number of fairly extensive outcrops of this formation scattered throughout an area of four hundred square miles in southern Levy and northern Citrus counties. The correlation of the outcrops with the subsurface Avon Park is proven by their microfauna, by similarity of lithology and by stratigraphical position beneath a thin limestone bed replete with characteristic echinoids, which bed in turn is known to underlie the Ocala limestone in core holes on the flanks of the Ocala uplift.

By most workers in Florida geology the Avon Park formation has been put in the Claiborne group although it has been rather generally felt that the evidence for Claibornian age was not complete. Lately the opinion that the formation ought to be reassigned to the upper Eocene or Jackson group has been gaining ground. Several of the recently found outcrops are rich in mollusks and echinoids. Although the study of this fauna will not be easy since the mollusks occur as moulds and calcite pseudomorphs and the echinoids are difficult to remove from the hard matrix, nevertheless it is reasonable to hope that with patient work this fauna may yet provide means for a final determination of the age of the Avon Park formation.

Since subsurface formation names cease to be valid when surface exposures have been found, the name Avon Park will have to be dropped. To take its place the writer proposes the name Gulf Hammock formation from the town of Gulf Hammock in Levy County where there are several good exposures.

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SCIENTIFIC BOOKS

AN OUTLINE OF POLITICO-GENETICS

The Dice of Destiny. An Introduction to Human Heredity and Racial Variation. By DAVID C. RIFE. Long's College Book Co., Columbus, Ohio, 1945. 163 pp. Price, $1.75.

THE calamity of the Second World War has awakened in many scientists a sense of social responsibility. It is this awakening, no doubt, that has prompted

[1] Paul L. Applin and Esther R. Applin, *Bull. Am. Assoc. Petrol. Geol.*, 28: p. 1686, 1944.

several geneticists to outline for popular consumption those aspects of their science which bear on man's social affairs. Among the books devoted to "politico-genetics," to use the author's apt phrase, the one under review is worthy of note. It is interestingly written, without cheap effects or exhibitionist wit, and with a simplicity and sincerity that will appeal to most readers. The parts of genetics that are not directly relevant to social problems are left severely alone, no matter how dear they may be to the hearts of specialists. For example, chromosomes are not mentioned. The core of the book is an account of what is known or conjectured about the inheritance of human traits and their modification by the environment. A good critical sense is displayed in the discussion of eugenical problems. The book concludes with chapters on "Race" and "Genes and Democracy." In the last named the author gives the reader a glimpse of his ideas on what the world of the future ought to be like.

The basic problem of politico-genetics is still the old nature-nurture puzzle. To be sure, we no longer divide human traits into sharply distinct categories of hereditary and environmental ones. Heredity determines the reactions of the organism to the environment. Yet, some genes produce the same character in all known conditions, while the expression of others is different in different environments. What we want to know is the amplitude of variation in the phenotype which a given genotype may develop in the environments actually available or potentially possible. The knowledge of human biology is, unfortunately, so incomplete that much scope is left for personal opinion of individual writers in this field. More than some, but less than other writers on politico-genetics, Professor Rife is inclined to regard heredity as being rigidly determinant. Heredity can hardly be taken to stand for "The Dice of Destiny" if its realization depends largely upon the environment which is in part controlled by human will. Although he quotes the data on the modifiability of the IQ, the author concludes that "heredity plays a major role in the determinations of how bright you are." Newman and his collaborators reached the conclusion, quoted by Rife, that "physical characteristics are the least affected by the environment, that intelligence is affected more, educational achievement still more, and personality and temperament the most of all." The role of heredity in the formation of the human personality is perhaps the central problem of the nature-nurture relationships. Observations and experiments show that heredity is very important in the determination of personality traits in domestic and wild animals. The author thinks that since "there is no reason to believe that man is a unique exception," it follows that "of the many components which enter into the determination of personality, it seems probable that some may be largely determined by heredity, and others by environment." Since races of animals frequently differ in personality traits, he believes that human races probably do so as well.

The frequently advanced argument that because psychic traits in animals are rather rigidly determined by heredity they are so determined in man deserves careful consideration. The analogy may be good, but arguments from analogy do not prove anything. The variability found in a living species is governed by natural selection according to the demands of the adaptation of the organism to its environment. Now, adaptation may be attained either through a reaction norm that responds to variations in the environment by evolving optimal phenotypes, or else through genotypic specialization for the particular environment in which the species normally lives. Which of these methods of adaptation is resorted to depends upon the inherent properties of the species, as well as upon the degree of stability, or changeability, of the environment. The greater the variety of conditions to which the organism is called upon to respond, the more versatile must be the reaction norm.

Man is a unique product of evolution in that he, far more than any other species, has escaped from the bondage of the physical and the biological into the social environment. Furthermore, human social environments are notable not only for their extreme complexity but also for the rapid changes to which immediate adjustment is demanded. Adjustment occurs chiefly in the psychic realm. The more advanced the social organization the less important are the physical characteristics. Because the changes in the human environment are not only rapid but diverse and manifold, genetic fixation of personality traits is decidedly undesirable. The survival, much more the success, of an individual in most human societies depends upon his ability rapidly to evolve behavior patterns which fit him to the kaleidoscope of circumstances he encounters. He must submit to some, rebel against others, and escape from still other situations. Individuals who display a fixity of response suffer under most forms of human society. An animal becomes adapted to its environment by evolving certain physical or behavioral traits; the adaptation of man consists chiefly in developing his inventiveness.

If social conditions should remain stable for many generations, genetic types adapted to different forms of social organization, and to different stations within a given society, might eventually arise. Such stability

does not obtain, however, and our western civilization is particularly noted for rapid transformations. When empires fall, or when ruling classes are overthrown, woe befalls their members unless they change their behavior speedily. A consistent genetic trend may, therefore, be expected in the evolution of human psychic traits, namely, that genotypes will be selected which permit more and more plasticity, and less and less fixity, in personality characteristics. The end result of this trend will be that the genotypic differences in personality traits will become quite unimportant compared to their phenotypic plasticity. This should not be construed to mean that mankind tends to become genetically uniform; the trend is not toward genotypic uniformity but toward phenotypic plasticity. Natural selection favors above all else the ability to become rapidly adjusted to circumstances which change not only from day to day but, in a modern society, from minute to minute. Genetic differences may be retained, provided that they permit themselves to be eclipsed by the phenotypic plasticity. Whether or not this trend has already run its full course must be settled by investigation and not by speculation. All that we can be reasonably sure of is that the evolutionary pattern of the human species is so different from those of the higher animals (not to speak of the lower ones) that judgments by analogy with respect to the psychic traits have little value. It may be that the non-pathological hereditary differences in behavior found among men are merely the uneroded remnants of genotypic specializations that were moulded by natural selection to fit the conditions of ages long past. Genotypes now emerging will perhaps predispose every individual to respond to every challenge that his environment may offer as a social rather than a solitary being.

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COSMIC RAYS

What Are Cosmic Rays? Revised and enlarged American edition. By PIERRE AUGER. Translated from the French by Maurice M. Shapiro. vii + 128 pp. 22 plates. Chicago: University of Chicago Press. 1945. $2.00.

THIS book, as stated in the translator's preface, is written "primaily for the reader who lacks a technical knowledge of physics, but who wants to keep in touch with current developments in science." It represents a revised and extended presentation of a book entitled "Rayons Cosmiques," published by the Presses Universitaires de France, Paris, 1941.

The first chapter, "Story of Discovery," introduces briefly the fundamental concepts associated with ionization and allied phenomena, together with their measurement, and leads up to the problem of an extra-terrestrial radiation. The second chapter, "The Heroic Epoch," traces the main steps which have been concerned with unravelling the general nature of the cosmic radiation. The third chapter, "Showers, Pairs, Bursts, Stars," enters into greater detail concerning the phenomena covered in its title. The fourth chapter, "Time Takes Its Toll of Cosmic Rays," discusses in further detail the nature of the particles which are associated with cosmic ray phenomena and the energies encountered in these particles. The last chapter, "The Sky's the Limit," deals further with cosmic-ray energies, particularly in relation to the evidence provided by "extensive showers," and further discussion is given of the extra-terrestrial origin of the primary cosmic ray particles and of the origin of the particles formed in the atmosphere, together with the interrelationships of the various particles.

While the book is written in elementary style, very easy of comprehension by a person with a limited knowledge of physics, it will not be so readily understood by the layman, to whom such expressions as "field," "electron volt energies," etc., represent an unfamiliar language. The style is vivacious and entertaining. Naturally, there are lacunae. In a small book of 128 pages one can hardly expect an approach to completeness of citation of the various experiments and ideas which have played a part in our present understanding of cosmic rays.

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